REMARKS

The Claimed Invention

Claims 74, 81, 87, 93, 99-104, 106-114 and 117-119 are pending in this application.

These claims define methods of treatment using one of two compounds or their pharmaceutically acceptable salts. A salt of one of these compounds, *N*-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea is the drug Nexavar®. The other compound, *N*-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(carbamoyl)-4-pyridyloxy) phenyl) urea is a derivative thereof.

Nexavar® has been approved for the treatment of renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) in the United States and was the first drug ever approved for the treatment of these cancers. It has been tested in various clinical trials for other cancers as shown by the publications made of record earlier.

There are claims to using one of these two compounds to treat a solid cancer (claims 74, 99, 106 and 110) to treating a carcinoma, myeloid disorder or adenoma (claims 81 and 107) to treat a carcinoma of the lung, pancreas, thyroid, bladder or colon (claims 87 and 108) and to treat a specific cancer (claims 100, 101, 102, 103, 104, 109, 110, 112, 113, 114, 115, `118 and 119). There is also a claim to inhibiting raf-kinase in a human or mammal by administering one of these two compounds (claim 117).

These two compounds are exemplified in the specification as entries 42 and 43 and each was found to inhibit the enzyme raf kinase (see page 2, line 10) using assays such as the assays disclosed in the specification on pages 94-96. As discussed in the background of the invention, raf inhibition was correlated with the inhibition of growth of a variety of tumor types at the time of the invention, see Kolch et al. (*Nature* **1991**, *349*, 426-28) and Monia et al., (Nat. *Med.* **1996**, *2*, 668-75).

Rejection under 35 U.S.C. §112, first paragraph

Claims 74, 81, 87, 93, 99-103, 106-114 and 117 stand rejected under 35 U.S.C. §112, first paragraph.

The Examiner has acknowledged that the specification is enabling for the treatment of carcinoma of the colon. With such a finding, Applicants submit all of the treatment methods claimed herein are clearly enabled. No evidence has been presented to question the teachings within the specification or to question the state of the art so as to support the rejection.

In alleging the specification fails to enable the claimed methods, the Examiner has not given any weight to the assay demonstrating the raf kinase activity of the two compounds recited in the claims. The examiner has ignored the state of the art at the time of the invention which taught the correlation of raf inhibition with the inhibition of the growth of a variety of tumor types (Monia et al.), the blocking cell proliferation (Kolch et al.) and the reversion of transformed cells to the normal growth phenotype (Daum et al., Fridman et al).

The Examiner has found these teachings to be insufficient requiring that the state of the art must clearly correlate the assays employed in the specification and clinical efficacy for treatment of the claimed diseases. Such a showing is unnecessary where there is no evidence that the results of the assay are inaccurate or are not reasonably correlated with efficacy. The specification is objectively enabling. One skilled in the art would assume the assignee, a pharmaceutical manufacturer, would use assays which were reasonably correlated with efficacy to find and invest in new products such a Nexavar®. Should there be any doubt; the specification teaches that the raf kinase assay does identify efficacious compounds based on the treatment of the tumor cell lines HCT116 and DLD-1, which was found to be sufficient to enable the methods for treating carcinoma of the colon.

The examiner claims the absence of a state of the art reference clearly establishing correlation between the assays employed and clinical efficacy is sufficient evidence to support the rejection for non-enablement. Silence in the art is not evidence that applicant's novel and unobvious methods are not enabled.

Furthermore, the art is not silent on his issue. Monia et al (1996) teaches there is correlation between raf kinase inhibition and the treatment of various conditions. The fact that the particular raf kinase assay described in the specification has not been shown to provide active compounds is simply a technicality. If there were any basis to question the raf activity of the two compounds recited in the claims, the cellular assay described in the specification confirms they have efficacious activity.

No evidence has been presented to refute the findings or conclusions made in the publications by Monia et al., Kolch et al. Daum et al. and Fridman et al. The language the examiner cites within Monia at page 668 does not raise any questions regarding the correlation between raf kinase inhibition and the treatment of various cancers and does not raise any questions that the assay described in the specification does not identify raf kinase inhibitors.

Monia clearly suggests there is a correlation between raf kinase inhibition and the treatment of various cancers at p.673, col. 2, lines 17-21, which states:

> The recent discovery that raf kinases function in part as downstream mediators of ras oncogene action suggests that inhibitors of raf gene expression may prove useful in the treatment of ras-dependent tumors.

Similarly, the language quoted from the Cecil reference is only a general commentary and does not pertain to raf kinase inhibitors or to assays which identify raf kinase inhibitors. The language does not refute the strong teachings of this correlation by Monia et al., Kolch et al. Daum et al. and Fridman et al. and the data within these publications which demonstrates this correlation.

The examiner acknowledges that the specification is enabling with respect to the treatment of carcinoma of the colon based on a cellular assay. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the other recited cancers with one of the two compounds named. Explicitly providing dedicated assays for each form of cancer is not necessary to enable the methods claimed. See, for example, *In re Howarth,* 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art.) In addition, performing such cellular assays would be absolutely routine in the field.

The examiner notes that many of the references cited in the Information disclosure statement are published after the filing date of the instant application. These are provided to show the teachings of Monia et al., Kolch et al., Daum et al. and Fridman et al, at the time of the invention, have not been refuted and that research consistent with their teachings continues.

Furthermore, not all of the references cited in the IDS were published after the filing date of this application. For example, Monia presented a paper in 1997 with data showing that the raf kinase inhibitor ISIS 5132 exhibited anti-tumor activity in varying tumor types such as lung, prostate, bladder, breast, melanoma, colon and small-cell lung. There are also reports by Monia et al. that the raf kinase inhibitor ISIS 5132 was in fact administered to patients with various diseases in clinical trials (renal cancer, colon cancer, melanoma, lymphoma, ovarian cancer, non-small cell lung cancer, small cell lung cancer, mesothelioma, colorectal cancer and sarcoma).

In addition, the references WO 98/22103, US Patent No. 6,204,267 and US Patent No. 6,180,631, which disclose the benzamide and azaquinoxaline raf kinase inhibitors as effective against a variety of diseases, were filed prior to the filing date of this application and represent the state of the art on filing this application

These documents illustrate that one skilled in the art would have no reason to doubt the teachings within the specification that the raf kinase activity of the two compounds recited in the claims was indicative of their ability to treat various diseases. Applicants maintain that the express disclosure within the specification is sufficient to enable the claims herein and that further assays or data to support the methods of treatment are not necessary. Based on the teachings within the art of the broad spectrum of activity of raf kinase inhibitors, one skilled in the art would recognize that the compounds recited in the claims herein having raf kinase activity would be effective in treating the diseases claimed.

Dependent claims

Claims 87, 93, 100-103,108, 109 and 111-114, name specific cancers and are clearly enabled by the specification in view of the state of the art. The art has correlated raf kinase activity specifically with the treatment of myelogenous

leukemias and carcinoma of the lung, pancreas, thyroid, bladder and colon such that method claims 87, 93, 100-103, 108, 109, 111-114, which recite these diseases, are clearly enabled.

Claim 117

Claim 117 is directed to a method of inhibiting raf -kinase in a human or other mammal with one of the two compounds listed. No reasons have been given for rejecting this claim as not enabled. The claim has been improperly characterized as a reach through claim. The claim does not define a research tool (assay) or a method of treatment by function alone, i.e., the function of inhibiting raf kinase. The claim has structure limitations in naming two compounds and in doing so does not claim unknown subject matter. In that the claim does not encompass unknown subject matter, the requirements of 35 USC§ 112, first and second paragraphs are met.

The specification provides sufficient guidance to prepare the two urea compounds and also provides sufficient guidance on how to prepare and administer compositions with these compounds, including dosages. The specification also shows that the free base of these compounds, compounds 42 and 43, inhibit raf kinase in the assays disclosed.

The examiner has not identified any element of the claim for which the disclosure is allegedly deficient and has not identified any claim term, which is allegedly indefinite. Instead, the examiner reads limitations into the claim regarding the treatment of diseases. Incorporating limitations into a claim is improper, *See Phillips v. AWH Corp.,* 415 F.3d 1303, 1313, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005) (en banc) and inconsistent with the MPEP. MPEP 2111.01 states "words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification" (*See In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989)) and "it is important not to import into a claim limitations that are not part of the claim."

In that there is no basis for referring to the specification for the meaning of any claim term and there clearly is no basis for reading treatment limitations into the claim, the rejection of claim 117 should be withdrawn for these reasons alone.

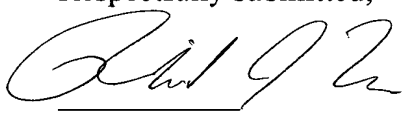
For the reasons indicated above, Applicants maintain that they have provided more than adequate guidance and examples to enable the claimed invention and submit all claims meet the requirements of 35 U.S.C. §112, first and second paragraphs.

Double Patenting

Claims 74, 81, 87, 93, 99-104 106-115 and 117-119 have been rejected under the doctrine of obviousness type double patenting over claims 38, 89-91 and 121 in US Serial No. 10/042,226. When the claims herein are otherwise allowable, applicants will address this rejection by either filing a terminal disclaimer over US Serial No. 10/042,226 or cancelling claims 38, 89-91 and 121 therein.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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